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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,777	07/19/2004	John Robert Birch	4145-14	5040

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EXAMINER	
MCGILLEM, LAURA L	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 05/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/501,777	BIRCH ET AL.	
	Examiner	Art Unit	
	Laura McGillem	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-8 and 10-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-8 and 10-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 July 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

It is noted that claims 1 and 3 have been amended, claims 2 and 9 have been cancelled and claims 10-15 have been added in the amendment to the claims filed 2/21/2006. A supplemental amendment was filed on 3/26/2006 to amend claims 12-15 and add claims 16-24. Claims 1, 3-8 and 10-24 are under examination.

Specification

It is noted that the abstract has been amended to remove legal phraseology and therefore, the objection to the specification has been withdrawn.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3, 7-8, 10, 12 and 19 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent 6,750,041 (Hollis et al) as evidenced by Abbas et al, (Cellular and Mol. Immunology. 2nd Ed. 1994. W.B. Saunders Co., Philadelphia, p.92). New claims 10, 12 and 19 are now added to this rejection.

Applicants submit that the rejection has been obviated by the amendment to claim 1 to incorporate the details of novel claim 2 (e.g. located on more than one DNA construct).

Applicants' arguments filed 2/21/2006 have been fully considered but they are not persuasive. Applicants' arguments are based on the intended limitation of the claimed cell by locating the claimed exogenous DNA sequences on more than one DNA construct.

However, claim 1 presents alternative limitations that can be interpreted in two ways because of the words "or" and "and".

In one interpretation, the cell can be transfected with:

an exogenous DNA sequence encoding a protein OR

an exogenous DNA sequence capable of altering the expression of an endogenous gene encoding a protein AND an exogenous DNA sequence encoding a glutamine synthetase,

meaning that a glutamine auxotropic human cell can be transfected with "an exogenous DNA sequence encoding a protein" only and still meet the limitations of the claim.

In a second interpretation, the cell can be transfected with:

an exogenous DNA sequence encoding a protein OR an exogenous DNA sequence capable of altering the expression of an endogenous gene encoding a protein

AND an exogenous DNA sequence encoding a glutamine synthetase,

meaning that a glutamine auxotropic human cell can be transfected with an exogenous DNA sequence encoding a protein AND an exogenous DNA sequence encoding a glutamine synthetase, OR an exogenous DNA sequence capable of altering the expression of an endogenous gene encoding a protein AND an exogenous DNA sequence encoding a glutamine synthetase and still meet the limitations of the claim. Claim 1 also recites the phrase "wherein these exogenous DNA sequences" and does not place a limitation on what combination of the three claimed exogenous DNA sequences must be located on more than one construct. For example, the exogenous DNA sequence encoding a protein is located on one DNA construct and an exogenous DNA sequence capable of altering the expression of an endogenous gene and an endogenous gene encoding a glutamine sequence is located on a second construct. Therefore, the glutamine-auxotropic human cells transfected with a recombinant expression plasmid comprising immunoglobulin light and heavy chain transcription units (see Hollis et al, column 6, lines 5-11, in particular), reads on the first interpretation of the claimed glutamine-auxotropic human cells transfected with exogenous DNA sequence encoding a protein. The presence of the gene encoding glutamine synthase renders the cell capable of growing in a glutamine-free medium.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-8, 10-13, 16, 19-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/05267 (Brandt et al) in view of Pu et al (Mol. Biotechnol.1998. Vol. 10, pp.17-25). New claims 10-13, 16 and 19-24 are newly included in this rejection.

Applicants submit that the rejection has been obviated by the amendment to claim 1 to incorporate the details of novel claim 2 (e.g. located on more than one DNA construct).

Applicants' arguments filed 2/21/2006 have been fully considered but they are not persuasive. As discussed above, claim 1 is written such that it encompasses multiple combinations of the claimed limitations and a broad interpretation of the location of exogenous DNA sequences on more than one DNA construct. In this instance, the claim is interpreted that the human cell comprises an exogenous DNA sequence capable of altering the expression of an endogenous gene and an endogenous gene encoding a glutamine sequence. Further, the breadth of the phrase "these exogenous DNA sequences are located on more than one DNA construct" can be interpreted that the sequences that are located on more than one construct are the alternative embodiments of the claims. For example, the exogenous DNA sequence encoding a protein is located on one DNA construct and an exogenous DNA sequence capable of altering the expression of an endogenous gene and an endogenous gene encoding a glutamine sequence is located on a second construct. Therefore, the claimed glutamine-auxotropic HT1080 cell comprising a heterologous expression control sequence active in the host cell wherein the host cell has an endogenous copy

of the target gene as taught by Brandt et al, combined with the glutamine-auxotropic dicistronic expression vector taught be Pu et al would still render the instant claims obvious in the embodiment discussed above.

Claims 10-11 are drawn to serum free and/or glutamine free culture medium used in the claimed process for production of a protein. Brandt et al teaches production of EPO in HT1080 cells grown in suspension cultures in serum free medium. Pu et al teach that cells comprising glutamine synthase as a selection marker are grown in glutamine free medium. Combination of these methods wherein the culture medium used in the claimed process is serum-free and glutamine free would be obvious for reasons discussed in the Office action mailed 10/20/2005.

Newly added claims 12 -13 and 16 add limitations to the claimed glutamine auxotropic human cell and process of producing an Erythropoietin wherein the produced protein is a glycosylated protein and specifically a sialylated protein. Brandt et al teach that it is desirable to have a human EPO protein produced with a comparable glycosylation pattern, especially in regard to sialic acid residues. It has been previously discussed that the HT1080 cells taught by Brandt et al read on an immortalized fibrosarcoma HT1080 cell line.

Claims 14-15 and 17-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/05267 (Brandt et al) in view of Pu et al (Mol. Biotechnol.1998. Vol. 10, pp.17-25) and further in view of Hermentin et al (U.S. Patent No. 6,096,555).

Applicants claim a cell and a process for the production of a protein comprising culturing a glutamine-auxotropic human cell in glutamine free medium and recovering the expressed sialylated protein comprising tri-, tetra- or pentasialo glycoforms. The sialylation is defined by an N-glycan charge.

As discussed previously, Brandt et al teach an HT1080 cell line which is used to express a target DNA to produce proteins such as EPO, by transfecting a host cell line with DNA constructs including a heterologous expression control sequence which is active in the host cell, wherein the host cell has an endogenous copy of the target gene (see page 5, (a)-(f), page 6, 2nd paragraph and page 11, Example 2, for example), which reads on a glutamine-auxotropic human cell line or an immortalized fibrosarcoma HT1080 cell line, which is transfected with an exogenous DNA sequence capable of altering the expression of an endogenous gene encoding a protein. Brandt et al teach that the cells were cultured to produce the target protein, which was then recovered and quantified from the cell supernatant (see page 8, paragraph 1.4, for example), which reads on a process for the production of a protein in a glutamine-auxotropic human cell and recovery of the protein. Brandt et al also teach that the target protein EPO is glycosylated (see page 10, paragraph 1.7, for example), which reads on a process for production of a protein wherein the protein is glycosylated.

Brandt et al do not teach that the glutamine-auxotropic human cell is transfected with an exogenous DNA sequence encoding a glutamine synthetase for positive selection of glutamine-auxotropic human cells. Brandt et al do not teach that sialylation

is defined by N-glycan charge or that the sialylated protein comprises tri-, tetra- or pentasialo glycoforms of N-glycan.

As previously discussed, Pu et al teach protein expression using glutamine synthetase as a selection marker on a dicistronic expression vector comprising the glutamine synthetase gene and a gene for interleukin-4 receptor transfected into CHO cells grown in glutamine- free medium (see page 18, left column, 1st full paragraph, and right column, paragraph 2.2, for example). Pu et al do not teach that sialylation is defined by N-glycan charge or that the sialylated protein comprises tri-, tetra- or pentasialo glycoforms of N-glycan.

Hermentin et al teach a process for characterizing the glycosylation of glycoproteins based on a hypothetical charge number N. Hermentin et al teach that it is important to reliably determine the degree of glycosylation or sialylation in glycoproteins, such as erythropoietin, in order to gauge bioavailability/biological activity of a protein for therapeutic use. Hermentin et al discloses that when erythropoietin is incompletely glycosylated, it is quickly cleared from the blood circulation and would not be biologically useful (see column 1, lines 6-15, 28-45 and column 2, lines 14-25, for example). Hermentin et al teach that it is crucial to determine the distribution of glycan groups exhibiting differing degrees of sialylation to be able to index the bioavailability of a glycoprotein. Hermentin et al teach that the N charge of a glycoprotein is determined in part by determining the percentage of trisialo, tetrasialo and pentasialo ranges (see column 3, lines 27-50, column 4, lines 27-35, column 5, lines 4-12, for example). Hermentin et al teach that the N-glycan charge value was determined for erythropoietin

and erythropoietin is comprised of trisialylated N-glycans and tetrasialylated glycans (see column 12, lines 43-52, for example), which reads on erythropoietin as a sialylated protein comprising tri and tetrasialylated glycoforms defined by N-glycan charge and a process of defining sialylation by N-glycan charge.

It would have been obvious to one of ordinary skill in the art to modify the teachings of Brandt et al to use a glutamine synthetase selection system taught by Pu et al to produce a target protein in HT1080 cells because Brandt et al teach that the positive selection marker can be any selection marker suitable for use in eukaryotic cells to convey a selectable phenotype including auxotrophy (see page 5, 4th paragraph, in particular). Pu et al teach that it is advantageous to use a glutamine synthetase selection over other commonly used selection markers because clones can be selected more rapidly and a wider host cell range can be used. The motivation to use glutamine synthetase selection in HT1080 cells is the expected benefit as suggested by Brandt et al and exemplified by Pu et al of the speed of clone selection and amplification, and a potential wider range of host cells for target protein expression.

It would have been obvious to the skilled artisan to determine the N-glycan charge for the erythropoietin because Hermentin et al teach that it is important to know the degree of glycosylation of recombinant therapeutic proteins such as erythropoietin, since slightly altered glycosylation patterns can drastically effect the activity of the therapeutic protein. The motivation to do so is the expected benefit of being able to determine the degree of glycosylation in a simple reliable manner suitable for replacing the methods previously known in the art for determining the bioavailability of a

therapeutic protein before use. There is reasonable expectation of success in combining the methods of Brandt et al, Pu et al and Hermentin et al to use a glutamine- auxotropic human cell transfected with an exogenous DNA sequence encoding a glycoprotein, such as erythropoietin, to produce and recover erythropoietin and determine its bioavailability via N-glycan charge, because these methods have worked before in the cited references. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the invention was made, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura McGillem whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DANIEL M. SULLIVAN
PATENT EXAMINER

Laura McGillem, PhD
5/26/2006